



Immune-complex deposits in anti-neutrophil cytoplasmic antibody associated crescentic glomerulonephritis; a report of two cases

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Abstract

Anti-neutrophil cytoplasmic antibody (ANCA)-associated crescentic glomerulonephritis is an important cause for rapidly progressing glomerulonephritis. It is generally classified under pauci-immune glomerulonephritis. However, 12%-18% of ANCA-associated crescentic glomerulonephritis show immune-complex deposits causing a diagnostic dilemma. We report 2 cases of ANCA-mediated glomerulonephritis with associated immune-complex deposits. First case is a 19-year-old female patient presented with fever and bilateral lower limb purpura since one day. Immunologic work-up was normal except positivity for cytoplasmic or c-ANCA by indirect immunofluorescence (IF). Kidney biopsy showed presence of segmental cellular crescent with fibrinoid necrosis. IF showed strong fine granular positivity for IgG, IgA, C3, C1q, kappa and lambda along the glomerular capillary walls. Second case is a 20-year-old male presented with low grade fever for last one month and vomiting for last two days. Immunologic work-up was unremarkable except positivity for cytoplasmic or c-ANCA by indirect IF. Kidney biopsy showed 14 glomeruli of which 8 glomeruli showed cellular crescents. IF for IgG, IgA, C3, kappa and lambda was done, which showed strong fine granular positivity along the glomerular capillary walls. Both the cases were treated with intravenous methylprednisolone and oral prednisone on a weaning regimen, and monthly therapy of intravenous cyclophosphamide. The maintenance phase consisted of mycophenolate mofetil and oral prednisone administered in alternate-day low-dose regimen. Both the patients are on regular follow-up and are doing well. These immune-complexes act synergistically with ANCA to cause more severe damage to the kidneys with a poorer outcome. Thus a prompt diagnosis and management of these patients is crucial.

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated crescentic glomerulonephritis is an important cause for rapidly progressing glomerulonephritis. It is generally classified under pauci-immune glomerulonephritis (1) implying that there are no immune complex deposits detected by immunofluorescence (IF). However, rare cases of ANCA positive glomerulonephritis may show immune complex deposits creating a diagnostic dilemma. We hereby report a case of a 19-year-old female patient with ANCA-associated crescentic glomerulonephritis along with presence of immune-complex deposits.

Case 1

A 19-year-old female patient presented with

Key point

ANCA-associated crescentic glomerulonephritis is generally classified under pauci-immune glomerulonephritis. However, 12%-18% of ANCA positive glomerulonephritis may show immune complex deposits creating a diagnostic dilemma. Moreover these immune-complexes act synergistically with ANCA to cause more severe damage to the kidneys with a poorer outcome. Thus a prompt diagnosis followed by management is crucial in these patients.

fever and bilateral lower limb purpura since one day. On examination, these purpuras were non-blanchable, palpable without significant bilateral lower extremity pitting edema and minimal facial puffiness. There



was no significant past medical and family history. On general examination, she had pallor and her blood pressure was 130/90 mm Hg. On investigation, hemoglobin was 7.6 g/dl, total leucocyte count was 5.700/ μ L and platelet count of 2×10^3 / μ L. Urine analysis showed 1+ proteinuria with urine microscopy showing numerous RBCs. The patient was found to have elevated serum creatinine level of 4.2 mg/dL. Immunologic work-up showed normal C3 and C4 levels and negative antinuclear antibody (ANA), rheumatoid factor, anti-double stranded DNA antibody, antistreptolysin O, and negative viral serology (hepatitis B, C, and HIV). She was positive for cytoplasmic or c-ANCA by indirect IF.

Skin biopsy was done from the lower extremity lesion. Skin biopsy showed infiltration of the dermal vessel wall by lymphocytes and neutrophils along with fibrin deposition, consistent with small vessel vasculitis (Figure 1A). Thus, a clinical diagnosis of small vessel vasculitis, likely to be granulomatosis with polyangiitis (Wegener's) was made and a renal biopsy was performed.

Kidney biopsy was tiny and showed three glomeruli out of which one showed presence of segmental cellular crescent with fibrinoid necrosis (Figure 1B, 1C). Mild mesangial proliferation was also seen. Tubules showed red blood cell (RBC) cast. Blood vessels showed myointimal hyperplasia and one inter-lobar artery included in the biopsy showed intimal fibrosis occluding 50% of the lumen. Co-relating with the clinical and serological studies, a provisional diagnosis of rapidly progressing glomerulonephritis due to small vessel vasculitis was considered.

IF showed strong (3+), fine granular positivity for IgG, IgA, C3, C1q, kappa and lambda along the glomerular capillary walls (Figure 1D). IgM was negative. Possibility of lupus nephritis was excluded due to ANA negativity and positivity for ANCA.

Thus a final diagnosis of ANCA-mediated glomerulone-

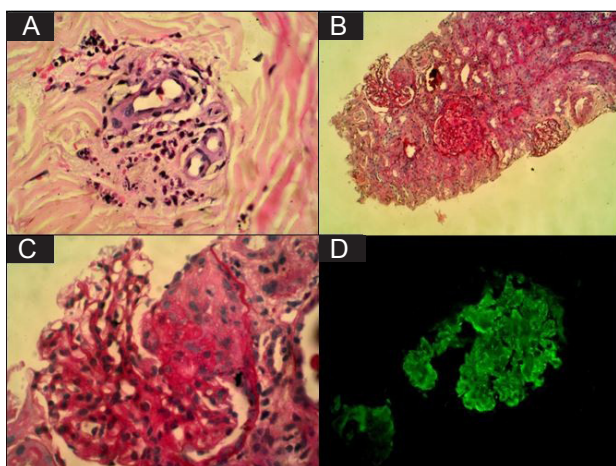


Figure 1. (A) Skin biopsy showing infiltration of the dermal vessel wall by lymphocytes and neutrophils (H & E, $\times 100$). (B) Kidney biopsy showing three glomeruli out of which one showed presence of segmental cellular crescent (H & E, $\times 40$). (C) Glomeruli showing presence of segmental cellular crescent with fibrinoid necrosis (PAS, $\times 400$). (D) IF showing strong (3+) fine granular positivity for IgG.

phritis with associated immune-complex deposits was made.

The patient received three pulses of intravenous methylprednisolone (1000 mg/d), with prednisone (1 mg/kg/d) on a weaning regimen, and monthly therapy of intravenous cyclophosphamide (1 gm/m²). The maintenance phase consisted of mycophenolate mofetil (1000 mg/d) and oral prednisone administered in alternate-day low-dose regimen. The patient tolerated the treatment without any complications and was discharged after 4 weeks with normal renal function tests. The patient is on regular follow-up and is doing well.

Case 2

A 20-year-old male presented with low grade fever for last one month. He complained of vomiting for last two days. There was no history of oliguria, dysuria, joint pain or rashes. There was no significant illness in the past or family history. On general examination, he had elevated blood pressure of 180/120 mm Hg. On investigation, haemoglobin was 8.7 g/dL, total leucocyte count was 6200/ μ L and platelet count of 2.5×10^3 / μ L. Urine analysis showed 3+ proteinuria with urine microscopy showing numerous RBCs. The patient was found to have elevated serum creatinine level of 3.5 mg/dL. Immunologic work-up was normal except positivity for cytoplasmic or c-ANCA by indirect IF.

After controlling his blood pressure, a kidney biopsy was performed under ultrasonography guidance. Kidney biopsy showed 14 glomeruli of which 8 glomeruli showed cellular crescents, 5 showed fibrocellular crescents and 1 showed fibrous crescent (Figure 2A, 2B). Fibrinoid necrosis was seen in 4 glomeruli. Tubules showed mild tubular atrophy (10%). Interstitium had moderate diffuse infiltration by lymphocytes. Blood vessels showed nodular hyalinosis (Figure 2C).

Nine glomeruli were seen in the IF section. IF for IgG, IgA, C3, kappa and lambda was done, which showed strong

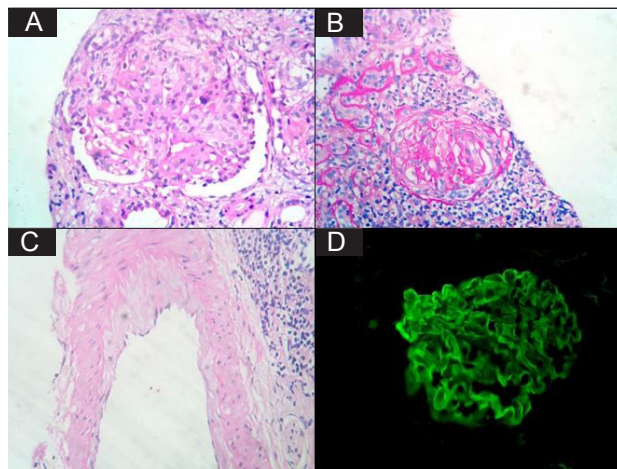


Figure 2. (A) Kidney biopsy showing cellular crescent (H & E, $\times 400$). (B) Glomeruli showing fibrocellular crescent (PAS, $\times 100$). (C) Blood vessels showed nodular hyalinosis (H & E, $\times 400$). (D) IF showing strong (3+) fine granular positivity for IgG.

(3+), fine granular positivity along the glomerular capillary walls (Figure 2D). IgM and C1q were negative.

A diagnosis of ANCA-mediated glomerulonephritis with associated immune-complex deposits was made.

The patient received three pulses of intravenous methylprednisolone (1000 mg/d), with prednisone (1 mg/kg/d). Monthly therapy of intravenous cyclophosphamide (1 gm/m²) was started after checking the total leucocyte count. Mycophenolate mofetil (1000 mg/d) and oral prednisone were administered in alternate-day low-dose regimen as part of maintenance therapy. At the time of discharge the patient was doing well with controlled blood pressure.

Discussion

ANCAs have been classically classified as c-ANCA which reacts with proteinase-3 and p-ANCA which reacts with myeloperoxidase. The two types occur with different frequencies in different small vessel vasculitis but are not specific for any specific vasculitis (2). However, ANCA positive, in appropriate clinical background does indicate presence of small vessel vasculitis even though it may not be possible to determine the specific disease entity (2).

ANCA-associated crescentic glomerulonephritis is an important cause of rapidly progressing renal failure and warrants early treatment. The classical picture of ANCA-associated glomerulonephritis is crescentic glomerulonephritis with associated fibrinoid necrosis and paucity of immune-complex deposits on IF. It has been known that 'pauci-immune' glomerulonephritis may show weak intensity immune deposits. Falk and Jennette have recommended that the term 'pauci-immune' be used when immune deposits are less than or equal to 2+ intensity on IF and absent on electron microscope (2).

ANCA-associated crescentic glomerulonephritis varies. Haas et al reported 12% of ANCA-associated crescentic glomerulonephritis had immune-complex deposits with $\geq 2+$ staining (3). Neumann et al reported that 18% of patients with ANCA-glomerulonephritis had $\geq 2+$ immune deposits on IF (4).

The exact importance of presence of these immune-complex deposits is not known. It is believed that these immune-complexes act synergistically with ANCA to cause more severe damage to the kidneys (5). In accordance with this theory, Haas et al and Neumann et al have found in their study that patients with ANCA positive glomerulonephritis with immune-complex deposition showed significantly greater proteinuria than the patients without the deposits (3,4). Also there have been studies using mice model which have showed that there is synergistic effect of immune-complex deposition with ANCA positivity in causing glomerular injury. Another possibility raised is that these cases represent ANCA positive crescentic glomerulonephritis superimposed on a pre-existing immune-complex mediated glomerulonephritis (6,7). ANCA

positivity has been reported in association with PIGN (4), IgA nephropathy (6), membranous nephropathy (7) and lupus nephritis (8,9).

Conclusion

Presence of immune-complex deposits in a case of crescentic glomerulonephritis does not exclude a diagnosis of ANCA-associated crescentic glomerulonephritis. An attempt should be made to identify an underlying immune-complex mediated disease entity, if any. In fact, presence of immune-complex in patients with ANCA positivity may lead to a more severe disease with poorer outcome.

Authors' contribution

All authors contributed equally to the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

Ethical considerations

Ethical matters such as (plagiarism, misconduct, data fabrication, falsification, and double publication or submission) have been thoroughly controlling by all authors.

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